IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants:	J. Rine et al.	Attorney Docket No.	UOCB118456
Application No:	10/038,206	Group Art Unit: 1631 / Confirmation No.:	1317
Filed:	January 2, 2002	Examiner:	John S. Brusca
Title:	SYSTEMS FOR GENERATING AND ANALYZING STIMULUS-RESPONSE OUTPUT SIGNAL MATRICES		

APPELLANT'S APPEAL BRIEF

Seattle, Washington
April 16, 2007

TO THE COMMISSIONER FOR PATENTS:

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I. REAL PARTY IN INTEREST

Regents of the University of California, a California non-profit organization, having a place of business at 300 Lakeside Drive, 22nd Floor, Oakland, California 94612, is the assignee of the entire interest of the appealed subject matter.

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II. RELATED APPEALS AND INTERFERENCES

There are none.

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III. STATUS OF CLAIMS

Claims 38-85 are pending in the application. All stand rejected under 35 U.S.C. § 103(a). Claims 38-85 are appealed. The table below indicates their status.

Claim(s)	Status	Appealed
1-37	Canceled	No
38	Rejected	Yes
39	Rejected	Yes
40	Rejected	Yes
41	Rejected	Yes
42	Rejected	Yes
43	Rejected	Yes
44	Rejected	Yes
45	Rejected	Yes
46	Rejected	Yes
47	Rejected	Yes
48	Rejected	Yes
49	Rejected	Yes
50	Rejected	Yes
51	Rejected	Yes
52	Rejected	Yes
53	Rejected	Yes
54	Rejected	Yes
55	Rejected	Yes
56	Rejected	Yes
57	Rejected	Yes
58	Rejected	Yes
59	Rejected	Yes
60	Rejected	Yes
61	Rejected	Yes
62	Rejected	Yes
63	Rejected	Yes
64	Rejected	Yes
65	Rejected	Yes
66	Rejected	Yes
67	Rejected	Yes
68	Rejected	Yes
69	Rejected	Yes

Claim(s)	Status	Appealed
70	Rejected	Yes
71	Rejected	Yes
72	Rejected	Yes
73	Rejected	Yes
74	Rejected	Yes
75	Rejected	Yes
76	Rejected	Yes
77	Rejected	Yes
78	Rejected	Yes
79	Rejected	Yes
80	Rejected	Yes
81	Rejected	Yes
82	Rejected	Yes
83	Rejected	Yes
84	Rejected	Yes
85	Rejected	Yes

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IV. STATUS OF AMENDMENTS

The application was rejected in an Office Action dated August 20, 2004. Thereafter, an Amendment and Response to the non-final Office Action was mailed on February 4, 2005, and entered into the file. The application was finally rejected in a paper dated April 6, 2005. An appeal brief was filed on July 19, 2005. A non-final Office Action was mailed on March 7, 2006, in which the Examiner re-opened prosecution. Thereafter, an Amendment and Response to the non-final Office Action was mailed on June 7, 2006 and entered into the file. The application was finally rejected in a paper dated August 18, 2006. A first Advisory Action was mailed on November 22, 2006. A telephonic interview with the Examiner occurred on January 22, 2007. A second Advisory Action was mailed on January 30, 2007. A second telephonic interview with the Examiner occurred on January 30, 2007. An amendment to Claim 69 after final rejection was mailed on February 15, 2007. A third Advisory Action was mailed on March 1, 2007 indicating that the amendment to Claim 69 would be entered for the purpose of appeal, and that the rejection of Claim 69, as amended under 35 U.S.C. § 101, was withdrawn. A copy of the claims, as amended, is attached in the Claims Appendix.

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V. SUMMARY OF CLAIMED SUBJECT MATTER

There are three independent claims on appeal, Claims 38, 56, and 70. Claim 38 is directed to a method for analyzing the effects of subjecting a living thing to a stimulus. In the practice of the method, physical signals are detected from a plurality of units ordered in a probe matrix. (Specification, page 5, line 28, to page 6, line 12; FIGURE 2.) Each unit of the plurality of units confines a probe (*e.g.*, a DNA molecule) comprising a pre-determined sequence of nucleotides. (Specification, page 5, lines 15-25.) Each of the pre-determined sequences is hybridizable with a different identified gene (or transcript thereof, or cDNA derived therefrom) of the living thing. (Specification, page 8, line 17, to page 9, line 1.) The probe matrix is contacted with gene transcripts or cDNA derived from the living thing subjected to the stimulus, and the resulting physical signals are transduced into electrical output signals. (Specification, page 5, line 28, to page 6, line 17; FIGURE 2; FIGURE 4.) Each electrical output signal is stored in digital form in an output signal data structure, wherein each stored digital signal is associated (i) with the stimulus; and (ii) with the identity of the identified gene. (Specification, page 6, line 22, to page 7, line 8; page 13, line 28, to page 14, line 13; FIGURE 1; FIGURE 2.) The effect of the stimulus on the living thing is analyzed by comparing the stored output signal data structure with an output signal data structure database, wherein the output signal data structure database comprises a plurality of output signal data structures stored in a computer memory. (Specification, page 7, lines 8-30; FIGURE 5.)

Claim 56 is directed to a method for producing an output signal data structure database recording the effect of subjecting a living thing to a plurality of stimuli. In the practice of the method, physical signals are detected from a plurality of units ordered in a probe matrix. (Specification, page 5, line 28, to page 6, line 12; FIGURE 2.) Each unit of the plurality of units confines a probe (*e.g.*, a DNA molecule) comprising a pre-determined sequence of nucleotides. (Specification, page 5, lines 15-25.) Each of the pre-determined sequences is hybridizable with a

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different identified gene (or transcript thereof, or cDNA derived therefrom) of the living thing. (Specification, page 8, line 17, to page 9, line 1.) The probe matrix is contacted with gene transcripts or cDNA derived from the living thing subjected to the stimulus, and the resulting physical signals are transduced into electrical output signals. (Specification, page 5, line 28, to page 6, line 17; FIGURE 2; FIGURE 4.) Each electrical output signal is stored in digital form in an output signal data structure, wherein each stored digital signal is associated (i) with the stimulus; and (ii) with the identity of the identified gene. (Specification, page 6, line 22, to page 7, line 8; page 13, line 28, to page 14, line 13; FIGURE 1; FIGURE 2.) The steps of detecting, transducing, and storing for a plurality of stimuli are repeated to form an output signal data structure database. (Specification, page 13, line 28, to page 14, line 20.)

Claim 70 is directed to a method for determining a response profile for a stimulus. Physical signals are detected from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from the living thing subjected to the stimulus. (Specification, page 5, line 28, to page 6, line 12; FIGURE 2.) Each unit of the plurality of units confines a probe comprising a pre-determined sequence of nucleotides, and each of the pre-determined sequences is hybridizable with a different identified gene of the living thing, or with a transcript of the gene, or with cDNA derived from the gene. (Specification, page 5, lines 15-25; page 8, line 17, to page 9, line 1.) The physical signals are transduced into electrical output signals and stored in digital form in a stimulus response data structure, wherein each stored digital signal is associated (i) with the stimulus; and (ii) with the identity of the identified gene. (Specification, page 5, line 28, to page 6, line 17; FIGURE 2; FIGURE 4; page 6, line 22, to page 7, line 8; page 13, line 28, to page 14, line 13; FIGURE 1; FIGURE 2.) A response profile for the stimulus is determined by comparing the stimulus response data structure with a basal response data structure produced by carrying out the foregoing steps of detecting, transducing, and storing, except that the probe matrix contacted with gene transcripts

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or cDNA derived from the living thing is subjected to basal conditions. (Specification, page 14, line 21, to page 17, line 5; FIGURE 6; FIGURE 7.)

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VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

First Ground of Rejection - Claims 38-53, 55-66, 68-83, and 85

Claims 38-53, 55-66, 68-83, and 85 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al. (*Mammalian Genome 3*:609-619, 1992), in view of Granelli-Piperno et al. (*J. Exp. Med. 163*:922-937, 1986), in view of either Fodor et al., 1998 (U.S. Patent No. 5,800,992), or Fodor et al., 1991.

Second Ground of Rejection - Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al., in view of Granelli-Piperno et al., in view of either Fodor et al. 1998 or Fodor et al. 1991, as applied to Claims 38-53, 55-66, 68-83, and 85 above, and further in view of Watson et al. (*Molecular Biology of the Gene*, 4th ed., Benjamin Cummings, Menlo Park, 1987, pp. 550-594).

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VII. ARGUMENT

Rejections Under 35 U.S.C. § 103(a)

Claims 38-53, 55-66, 68-83, and 85

Claims 38-53, 55-66, 68-83, and 85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al., in view of Granelli-Piperno et al., in view of either Fodor et al. 1998 (U.S. Patent No. 5,800,992) or Fodor et al. 1991.

The Examiner has taken the view that Gress et al. discloses a method of assaying patterns of transcription by use of labeled cDNA from mouse and human cells by the use of a cDNA X-Y coordinate grid array of probes. Gress et al. is further cited by the Examiner as disclosing the importation of resulting data via an electrical signal of a Phosphorimager to a computer implemented relational database. The Examiner acknowledges that Gress et al. does not show (1) subjection of assayed cells to different stimuli; (2) comparison of the transcriptional profile of cells that have received different stimuli; (3) assay of discrete portions of the complete number of genes of the cell; or (4) use of probes with a predetermined sequence of nucleotides. The Examiner characterizes Granelli-Piperno et al. as disclosing that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression via intensity of a film image on an autoradiograph. Fodor et al. '91 or '98 are cited by the Examiner as disclosing a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. The Examiner then concludes that it would have been obvious to a person of ordinary skill to modify the method of Gress et al. by assaying cells that have received treatments with different drugs according to the method of Granelli-Piperno et al., because Granelli-Piperno et al. shows that such an analysis serves to gain insights on the mechanism of action of the drug. The Examiner takes the view that it would have been further obvious to assay additional numbers of genes as desired to determine the effect of a drug on

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additional genes. The Examiner further concludes it would have been obvious to make and use an array of probes with a predetermined sequence as disclosed by Fodor et al. '91 or '98. Applicants disagree with the Examiner's conclusions for the following reasons.

It is submitted that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the referenced teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); Manual of Patent Examining Procedure (M.P.E.P.) (8th ed., August 2001, rev. May 2004) Sections 706.02(j), 2142 and 2143. As stated in *In re Fritch*, 972 F.2d 1260, 1266, 23 U.S.P.Q.2d 1780, 1784, (Fed. Cir. 1992), it is impermissible to use the claimed invention as an instruction manual or "template" in attempting to piece together isolated disclosures of the prior art so that the claimed invention is rendered obvious.

It is submitted that a *prima facie* case of obviousness has not been established because (1) there is no motivation to modify Gress et al. as proposed by the Examiner, rather, Gress et al. actually teaches away from the present invention; (2) the modification of Gress et al. proposed by the Examiner would render the method of Gress et al. inoperable for its intended purpose, (3) impermissible hindsight reconstruction has been used to improperly combine elements from Gress et al. and Fodor et al. '98 or '91; and (4) even if improperly combined, the teachings of Granelli-Piperno et al. and either Fodor et al '98 or Fodor '91 fail to cure the deficiencies of Gress et al. because the combined teachings do not teach or suggest all the claim limitations.

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Gress et al. Teaches Away From the Claimed Invention

It is well established that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference." *In re Gurley*, 27 F.3d 551, 31 U.S.P.Q.2d 1130, 1131 (Fed. Cir. 1994).

It is submitted that the teachings of Gress et al. would not provide any expectation of success that would motivate one to modify the Gress et al. method in order to analyze the effects of subjecting a living thing to a stimulus comprising detecting physical signals from a plurality of units ordered in a probe matrix as claimed in the present invention. In fact, when read in its entirety, Gress et al. actually teaches away from the claimed invention because the method of Gress et al. is not suitable for measuring differences in gene expression and requires extensive use of controls due to the high level of background hybridization from polyA tails and repeated sequences, as described in more detail below.

The goal of the approach described in Gress et al. was to allow the initial characterization of large numbers of cDNA library clones with a minimal number of experiments (page 609, first column). In particular, Gress et al. discloses a method of hybridization fingerprinting analysis involving labeling total cDNA pools derived from different tissues and hybridizing the labeled cDNA pools to cDNA library arrays to *identify* clones in the cDNA library containing mRNA sequences expressed at *middle to high abundance* (Gress et al. at page 609, second column). As stated in Gress et al., the system was used successfully to analyze "clones *abundantly expressed* in several tissues that most likely code for proteins involved in structural and regulatory functions in every cell." (Page 610, first column). It is noted that although the method of Gress et al. was suitable for the purpose of identifying previously uncharacterized abundantly expressed clones, it appears that the method of Gress et al. would not be suitable for the detection of low abundance transcripts in a cDNA library. Thus, it would not be suitable for measuring differences in gene expression and therefore would not provide any expectation of success for use in the methods of

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the present invention. Moreover, because the method of Gress et al. was suitable for its intended purpose of clone identification, there is no motivation provided in Gress for a person of ordinary skill in the art to modify the method as proposed by the Examiner.

A further drawback to the Gress et al. method that would lead one away from use in the present invention is the requirement for numerous controls due to the high level of background hybridization. As noted by the Examiner, Gress et al. shows that polyA control probes hybridize non-specifically to many array cDNA probes. and that other cDNA probes in the array contained repetitive sequences that also caused non-specific hybridization. See Office Action mailed August 18, 2006, page 4. For example, as stated in Gress et al., "[a] polyA-homopolymer probe hybridized to a considerable number of clones identified with cDNA pools (30-40% for HFB and 7-12% for Drosophila; Table 1, Figs 1b and 3e)." As further stated in Gress et al., "a control hybridization with a PolyA homopolymer proved *essential*, as up to 45% of identified clones may appear positive by hybridization of labeled PolyA tails to large stretches of PolyT in the cloned cDNA." (Gress et al. at pages 615-616, emphasis added). In addition, Gress et al. states:

> [c]ontrol hybridization with total genomic DNA allowed the detection of additional clones positive owing to hybridization with other labeled repetitive sequences in the pool probe. An efficient elimination of all 'false positives' is possible only with the strategy presented here. Other groups have encountered the same problems and have tried to reduce them by different competition techniques (Dworkin and Dawid 1980, Crampton et al. 1980). Our experiments demonstrate that even a maximal competition with PolyA/PolyU-homopolymers and genomic DNA *is not sufficient to eliminate these background problems completely.*

(Gress et al. at page 616, first column, emphasis added.)

Also mentioned in Gress et al. is "the difficulty in comparing results with previous experiments (controls and hybridization fingerprints)." (Gress et al. page 617, second column.) Moreover, Gress et al. describes difficulties with regard to the computerized image analysis. For example, as described in Gress et al.:

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> [m]uch time and effort was invested in this part of the approach; in particular, the standardization and optimization of the image analysis system proved demanding. A large scale of grey values is generated in one single-tissue cDNA pool hybridization, and the determination of adequate grey value thresholds allowing one to distinguish between "positives and negatives" in each individual experiment is not a simple matter.

(Gress et al. at page 616, second column.)

Therefore, one would not be motivated to modify the methods of Gress et al. as proposed by the Examiner because of the limitations of the Gress method for measuring relative gene expression levels and due to the high background hybridization observed using the Gress method.

In response to the above arguments advanced by Applicants during prosecution, the Examiner has maintained the view that despite the necessity of controls, it is still possible to quantify levels of gene expression by the method of Gress et al., with particular reference to Figure 2 and Table 1. See Office Action mailed August 18, 2006, pages 7-8, and Advisory Action mailed January 30, 2007. In particular, the Examiner has stated:

> The Applicants state that Gress et al. does not show a quantitative response, however the signal level of hybridization to clones is determined as a grey level, and Table 1 shows data of colonies that have a level between cutoff values of the grey levels, which is a result made by a process of quantitative measurement of hybridization to clones. Furthermore Figure 2 shows grey levels of different colonies detected by different cDNA pools, which is also a quantitative result.

Page 2 of the Advisory Action mailed January 30, 2007.

Applicants disagree with the Examiner's interpretation that the method of Gress et al. provides quantitative measurement of gene expression. Applicants note that Table 1 does not describe a comparison of gene expression levels, but rather presents results showing the total number of uncharacterized cDNA clones on a nitrocellulose filter that hybridized to a panel of cDNA pools obtained from various tissues of various organisms. In fact, the results of Table 1 demonstrate that the Gress et al. method is not suitable for same-species analysis due to the high

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background hybridization resulting from repetitive sequences. The authors in Gress et al. acknowledge this drawback of the method, stating with regard to Table 1, "cDNA pool probes were preferentially prepared from a different species (*e.g.*, mouse) than the cDNA library (human) to reduce unspecific hybridization due to human-specific repetitive sequences (*e.g.* Alu)." See Gress et al., page 616, Column 1; page 612, Column 1. In contrast, the claimed invention is directed to "a method for analyzing the effects of subjecting a living thing to a stimulus comprising (a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus." See Claims 38, 56, and 70.

Moreover, it is apparent from the results in Table 1 that the nitrocellulose filters containing the cDNA pools described in Gress et al. contain numerous uncharacterized repetitive sequences and non-coding sequences that do not specifically hybridize to a transcript of an expressed gene. In this regard, Gress et al. states with reference to Table 1, "[a] large number of these positives could not be used for further analysis as they hybridized with one of the control probes as well (up to 45% for HFB and up to 16% for Drosophila)." Gress et al., page 612, Column 2. As further described, "[o]n average, one clone in a pool hybridized to 10-14 clones on each HFB library filter (Fig 5a and b)." Gress et al. at page 613, Column 2. In contrast, the present invention is directed to the use of a matrix comprising a plurality of units wherein each unit confines a probe comprising a predetermined sequence hybridizable with a different identified gene, transcript or cDNA derived from the gene of a living thing. See Claims 38, 56 and 70.

The Examiner has also relied on Figure 2 of Gress et al. as disclosing the ability to quantify levels of gene expression. Applicants also disagree with the Examiner's conclusion in this regard. Figure 2 merely shows the identification of *positive versus negative clones*, where positive clones were identified as having a level of expression detected over a chosen threshold

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value. As stated by the authors in Gress et al., Figure 2 shows "typical grey value patterns as produced by different cDNA pool and control hybridizations for a subset of HFB library clones." Gress et al., legend to Figure 2, page 614. All the grey values shown in Figure 2 representing various clones on the hybridization filter are expressed with a value represented as either "1X" (*e.g.*, positive) or "zero" (*e.g.*, negative) on a scale from zero to 2X. As further described in Gress et al.:

> [a] large scale of grey values is generated in one single-tissue cDNA pool hybridization, and the determination of adequate grey value thresholds *allowing one to distinguish between 'positives and negatives' in each individual experiment* is not a simple matter.

See Gress et al. at page 616, Column 2.

Therefore, it is submitted that Gress et al. teaches away from comparing transcript levels of a panel of genes from stimulated and unstimulated cells derived from a subject, as claimed.

The Examiner acknowledges that Gress et al. is silent with respect to the use of predetermined sequences; however, the Examiner argues that it would have been further obvious to modify the method of Gress et al. by using an array of probes which each have a pre-determined sequence as disclosed by Fodor et al., because Fodor et al. shows that such an array has the advantage of allowing the sequences detected in the sample to be mapped to a particular location of the genome of the organism sampled. Applicants disagree with the Examiner's conclusion.

One of skill in the art would recognize that in order to use an array of sequenced cDNA molecules in the practice of the Gress et al. method, the thousands of cDNA molecules that are to be arrayed on a substrate would first have to be sequenced. An array of cDNA-specific oligonucleotide hybridization probes could be used instead of the corresponding cDNAs, but each of the thousands of cDNA molecules would have to be sufficiently sequenced to identify an oligonucleotide sequence element that is unique to each cDNA, and that acts as a cDNA-specific

hybridization probe under defined hybridization conditions. Sequencing the thousands of cDNAs arrayed on a substrate in the practice of the Gress et al. invention would be unnecessary, and as described below, would actually render the method of Gress et al. unsuitable for its intended purpose of gene discovery.

It is submitted that there is no motivation provided in Gress et al. to modify the Gress et al. invention to incorporate sequenced array elements, because the use of sequenced array elements is not necessary for the successful use of the Gress et al. invention, and there is no incentive for one of ordinary skill in the art to unnecessarily expend considerable time and money sequencing thousands of array elements.

Obviousness cannot be established by combining teachings of prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art which would have made such combination appropriate. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.* 776 F.2d 281, 227 U.S.P.Q. 657 (1985); *See* also M.P.E.P. 2144.08, *In re Vaeck*, 947 F.2d at 493. (A proper obviousness analysis requires consideration of "whether the prior art would have revealed that in so making or carrying out the claimed invention, those of ordinary skill would have a reasonable expectation of success."). Accordingly, applicants submit that one of ordinary skill in the art would not be motivated to modify the Gress et al. invention as proposed by the Examiner because the Gress et al. teaches away from the present invention by describing the difficulty of obtaining reliable and reproducible gene expression data from the type of hybridization array described in Gress et al. (i.e., a cDNA library spotted in a 96 well plate). Moreover, the method of Gress et al. is described as being useful for detecting expression of genes abundantly expressed, and therefore would not motivate one to use the methods of Gress et al. to measure relative levels of gene expression.

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The Examiner's Proposed Modification Renders the Gress et al. Method Unsatisfactory for its Intended Purpose

It is well established that if a proposed modification would render a prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. See, *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984).

As described above, Gress et al. discloses a method for characterizing large numbers of cDNA library clones, and is useful, for example, to identify cDNA clones that are abundantly expressed in several tissues, and that are likely to encode proteins involved in structural and regulatory functions in every cell. The identified cDNA clones can then be partially sequenced, so as to allow the correlation of genomic mapping, transcriptional information and sequence information into a global data set (see Gress et al. at page 609, Column 1, last two sentences, and Column 2, first paragraph, last sentence; page 610, Column 1, second paragraph, last sentence). In the practice of the Gress et al. method, thousands of unidentified cDNA clones from human fetal brain, and from Drosophila embryos, are arrayed on a nitrocellulose filter, and hybridized against a labeled cDNA pool derived from mouse tissues. Partial sequence data for clones of interest are then generated (see Gress et al. at sentence spanning pages 617-618). It is noted that only a small number of Drosophila cDNA clones were actually sequenced in Gress et al. in order to demonstrate the applicability of the approach to the Drosophila genome; see Gress et al. at page 613, Column 2, first paragraph.). For example, Gress et al. explicitly states "[t]he approach presented here will be of special value in selecting clones for the generation of expressed sequence tagged sites (ESTs) for mapping and sequencing the human genome." See Gress et al. at page 617, Column 2.

The Examiner argues that it would have been obvious to modify the method of Gress et al. by using an array of probes which each have a pre-determined sequence as disclosed

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by Fodor et al., because Fodor et al. shows that such an array has the advantage of allowing the sequences detected in the sample to be mapped to a particular location of the genome of the organism sampled. The Examiner further argues that Gress et al. sequences selected clones to facilitate correlation of their results with other databases as shown in the abstract of Gress et al., and so it is therefore apparent that the prior art shows advantages and motivation for determining the sequence of elements of an array. The Examiner also argues that Fodor et al. has been cited to show that the prior art details a method to create an array with predetermined sequences at each element, which has the advantage of obviating subsequent sequencing to characterize elements of interest determined by the hybridization experiment.

Applicants submit that the Examiner's proposal to replace the thousands of unidentified cDNA clones that are arrayed on a nitrocellulose filter, or other substrate, as taught by Gress et al., with oligonucleotides having known sequences, would render the Gress et al. invention inoperable for its intended purpose. For example, in the Gress et al. publication, thousands of unidentified cDNA clones from human fetal brain, and from Drosophila embryos, are arrayed on a nitrocellulose filter, and hybridized against a labeled cDNA pool derived from mouse tissues. The strongly hybridizing clones are selected for sequencing because these are likely to encode highly expressed proteins that are involved in structural and regulatory functions in every cell, and which are conserved throughout a wide range of species. The successful practice of the Gress et al. method does not require any knowledge of the identity or sequence of the cDNA clones that are being sought. Indeed, it would be illogical to use probes of known sequence in order to determine which of the probes of known sequence will be sequenced.

Moreover, modification of the Gress et al. invention to replace the thousands of unidentified cDNA clones arrayed on a substrate with thousands of probes which each have a pre-determined sequence, as suggested by the Examiner, would only permit an investigator to identify the expression pattern of those clones in the pool that happen to hybridize to one of the

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pre-determined sequences. Clones that do not hybridize to one of the pre-determined sequences could not be screened using the modified method of Gress et al. Even if the pre-determined sequences were selected to hybridize to thousands of different expressed genes (or cDNAs derived therefrom), one of ordinary skill in the art would have to know at least part of the sequence of each of the thousands of different expressed genes (or cDNAs derived therefrom).

Consequently, applicants submit that it is not obvious to modify the Gress et al. method by incorporating the teachings of the Fodor et al. publication as suggested by the Examiner.

Impermissible Hindsight Reconstruction Has Been Used to Improperly Combine Elements From Gress et al. and Fodor et al.

It is well established that prior art references must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention. It is impermissible to pick and choose among individual parts of assorted prior art references to recreate the claimed invention. See, *e.g.*, *Azko N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1481, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 2490 (1987). Section 103 specifically requires consideration of the claimed invention as a whole. As pointed out recently by the Federal Circuit:

> [i]nventions typically are new combinations of existing principles or features . . . the 'as a whole' instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A+B+C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. Section 103 precludes this hindsight discounting of the value of new combinations by requiring assessment of the invention as a whole.

Ruiz v. A.B. Chance Company, 357 F.3d 1270, 69 U.S.P.Q.2d 1686, 1690 (Fed. Cir. 2004).

In the present case, the Examiner relies upon Gress et al. as disclosing a general method of assaying patterns of transcription by use of labeled cDNA from mouse and human cells by use

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of a cDNA X-Y coordinate grid array of probes. The Examiner characterizes Fodor et al. as showing throughout a method of making an array of polynucleotide probes of predetermined sequence by independent *in situ* stepwise synthesis of each oligonucleotide probe from the array.

Applicants submit that the Examiner does not give due consideration to where the references diverge and teach away from the claimed invention. Thus, for example, applicants submit that the Examiner does not give due weight to the fact that Gress et al. teaches screening thousands of unidentified cDNA clones, using an array of cDNA probes, in order to identify the most highly expressed clones, without biasing the result by selecting certain groups of clones that hybridize to probes having defined sequences. In contrast, Fodor et al. is concerned with the manufacture and use of arrays of probes having defined sequences that can be used to measure the level of expression of specific populations of nucleic acid molecules. Applicants submit that the purpose and focus of the Gress et al. and Fodor et al. publications are quite different, and that when the two publications are each read as a whole, there is no motivation to combine them, or to select individual elements of the disclosure of each of these publications and combine them.

Therefore, contrary to the Examiner's assertion that it would have been obvious for the skilled worker to modify Gress to result in the present invention, it is respectfully submitted that because the teachings of Gress et al. actually teach away from the claimed invention, there is no motivation to modify Gress et al. as suggested by the Examiner.

The Teachings of Granelli-Piperno et al. and/or Fodor et al. '98 or '91 Fail to Cure the Deficiencies of Gress et al.

The Examiner has acknowledged that Gress et al. does not show (1) subjection of assayed cells to different stimuli; (2) comparison of the transcriptional profile of cells that have received different stimuli; (3) assay of discrete portions of the complete number of genes of the cell; or (4) use of probes with a predetermined sequence of nucleotides. In addition, applicants wish to point out that Gress et al. also fails to teach or suggest (5) quantitative measurement of relative

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levels of gene expression; (6) comparison of a transcriptional profile within a species; or (7) storing in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated (i) with a stimulus; and (ii) with the identity of the identified gene.

It is submitted that the shortfalls of the Gress et al. reference are not cured by the teachings of Granelli-Piperno et al. and/or Fodor et al. '98 or '91, either alone or in any combination.

Granelli-Piperno et al. describes Northern blot analysis of nine lymphokine mRNAs known to be involved in T cell stimulation in order to compare expression of the lymphokine mRNA expression in terms of kinetics, mitogen requirements and sensitivity to cyclosporin A. It is noted that Granelli-Piperno et al. fails to teach or suggest at least the use of a matrix comprising a plurality of units wherein each unit confines a probe comprising a predetermined sequence hybridizable with a different identified gene, transcript or cDNA derived from the gene of a living thing, or storing in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated (i) with a stimulus; and (ii) with the identity of the identified gene, as claimed. In sharp contrast to the claimed invention, the methods described in Granelli-Piperno et al. relate to the use of a nitrocellulose filter containing total cellular RNA isolated from T cells that is hybridized with individual probes specific to nine genes known to be involved in T cell stimulation (see Granelli-Piperno et al., page 923, third paragraph). Moreover, as described above, there is no motivation to modify the method of Gress et al. with the teachings of Granelli-Piperno et al. because Gress et al. teaches away from the claimed invention. For example, one would not be motivated to compare stimulated and unstimulated cells from the same subject using the methods of Gress et al. due to the high background resulting from the numerous uncharacterized repetitive sequences, and due to the inability to quantitatively measure relative levels of gene expression. Therefore, one of skill in the art would not have a reasonable expectation

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of success. Finally, even if one were to improperly combine the teachings of Gress et al. and Granelli-Piperno et al., the references fail to disclose all the elements of the claimed invention.

Moreover, particularly regarding Claims 49-51, as well as Claims 63-65 and Claims 80-82, Granelli-Piperno et al., alone or in combination with the other references, does not render obvious these claims because Granelli-Piperno et al. only teaches studying the effect of the stimulus on the expression of a small subset of genes in a cell. The proposed motivation by the Examiner to modify the referenced teachings to assay additional numbers of genes does not derive from the references themselves. It is noted that there is no teaching or suggestion in Granelli-Piperno et al., or in any other reference cited by the Examiner, to detect physical signals from a plurality of units ordered in a probe matrix, wherein each unit confines a probe comprising a pre-determined sequence that is hybridizable to at least 0.5% of the genes of the living thing, in order to analyze the effects of subjecting a living thing to a stimulus as claimed. Rather, Granelli-Piperno et al. is a directed study specifically designed to analyze the effect of cyclosporin A on a set of nine different lymphokine mRNA levels (see page 922, third full paragraph). As described in Granelli-Piperno et al., cyclosporin A was already known to effect the expression of lymphokine mRNAs known to be involved in T cell stimulation (see Granelli-Piperno et al., page 922). Therefore, absent some suggestion to assay a wider array of genes, such as at least 0.5% of the genes of a living thing, to measure the effect of a stimulus on a living subject, there is no motivation or expectation of success to attempt to modify the method of Gress et al. with the teachings of Granelli-Piperno et al.

The Examiner cites Fodor et al. '91 or Fodor et al. '98 as teaching a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. The Examiner further takes the view that a modification of the array as proposed by the Examiner by use of predetermined sequences of probes shown in Fodor et al. '91 does not conflict with the purpose of Gress et al. of using the array for *identification* of highly expressed cDNA clones. Applicants

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respectfully disagree with the Examiner's conclusion in this regard. As described above, Gress et al. explicitly states that the approach is of value in *selecting clones for the generation of expressed sequence tagged sites* for mapping and sequencing the human genome. It is clear in Gress et al. that the objective is to identify previously uncharacterized clones that are expressed for *future* sequencing and analysis. Therefore, as noted above, the Examiner's proposed modification of Gress et al. to include the use of predetermined sequences would conflict with the stated purpose in Gress et al. of identifying and sequencing new, previously uncharacterized mRNA transcripts.

Moreover, it is noted that even if combined, which there is no motivation to do, none of the cited references, either alone or in any combination, teach or suggest the step of storing in digital form each electrical output signal in an *output signal data structure*, wherein each stored digital signal is associated: "(i) with said stimulus and (ii) with the identity of said identified gene" as required by independent Claims 38, 56 and 70. Therefore, even if improperly combined, the teachings of Granelli-Piperno et al. and either Fodor et al. '98 or Fodor et al. '91 fail to cure the deficiencies of Gress et al. because the combined teachings do not teach or suggest all the claim limitations.

In view of the foregoing arguments, applicants submit that Claims 38-53, 55-66, 68-83, and 85 are not obvious in view of Gress et al., in view of Granelli-Piperno et al., in view of Fodor et al. Applicants respectfully request that the Examiner's rejection of Claims 38-53, 55-66, 68-83, and 85 under 35 U.S.C. § 103(a) be withdrawn.

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al., in view of Granelli-Piperno et al., in view of either Fodor et al. 1998 (U.S. Patent No. 5,800,992) or Fodor et al. 1991, and further in view of Watson et al.

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The Examiner characterizes the rejected claims as being drawn to assays utilizing fungal cells and cites Watson et al., pages 573-575, for its teaching that these cells contain genes that are regulated by stimuli such as metabolites.

For at least the reasons set forth in connection with the rejection of Claims 38-53, 55-66, 68-83, and 85 under 35 U.S.C. § 103(a), it is submitted that it is not obvious to combine the teachings of Gress et al., Granelli-Piperno et al., or Fodor et al., as suggested by the Examiner. This deficiency is not cured by the teachings of Watson et al. Applicants respectfully request that the rejection of Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 under 35 U.S.C. § 103(a) be withdrawn.

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VIII. CLAIMS APPENDIX

1-37. (Canceled)

38. A method for analyzing the effects of subjecting a living thing to a stimulus comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the plurality of units confines a probe comprising a pre-determined sequence of nucleotides, and wherein each of said pre-determined sequences is hybridizable with a different identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

(b) transducing the physical signals into electrical output signals,

(c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

(d) analyzing the effect of said stimulus on said living thing by comparing the stored output signal data structure with an output signal data structure database, wherein the output signal data structure database comprises a plurality of output signal data structures stored in a computer memory.

39. The method of claim 38 wherein the probes are 24-240 nucleotides in length.

40. The method of claim 38 wherein the probes comprise lengths of nucleotide sequences selected so as to be hybridizable with a transcript or cDNA derived from said identified gene.

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41. The method of claim 38 wherein the probes comprise polynucleotide sequences not hybridizable to more than one contiguous gene of the living thing.

42. The method of claim 38 wherein the gene transcripts or cDNA derived from the living thing are labeled.

43. The method of claim 38 wherein the ordered units in a probe matrix comprise an ordered array of units identified by X and Y coordinates, and wherein output signal data structures comprise matrices with elements identified by the X and Y coordinates.

44. The method of claim 43 further comprising establishing a table relating the X and Y coordinates of each unit to the identity of said identified gene.

45. The method of claim 38 wherein the step of storing further comprises storing each digital signal in a computer readable memory.

46. The method of claim 38 wherein the probe matrix comprises oligonucleotide probes that are arrayed on a substrate.

47. The method of claim 38 further comprising a step of producing the output signal data structure database by a method comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to a stimulus, wherein each unit of the plurality of units confines a probe comprising a pre-determined sequence of nucleotides, and wherein each of said pre-determined sequences is hybridizable with a different identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

(b) transducing the physical signals into electrical output signals,

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(c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

(d) repeating steps of detecting, transducing, and storing for a plurality of stimuli to form an output signal data structure database.

48. The method of claim 47 wherein the probes comprise polynucleotide sequences not hybridizable to more than one contiguous gene of the living thing.

49. The method of claim 38 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

50. The method of claim 49 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 5% of the genes of said living thing, or with transcripts of at least 5% of said genes, or with the cDNA derived from at least 5% of said genes.

51. The method of claim 50 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 50% of the genes of said living thing, or with transcripts of at least 50% of said genes, or with the cDNA derived from at least 50% of said genes.

52. The method of claim 38 wherein the probe matrix comprises probes having sequences that are hybridizable with a functional class or subset of the genes of said living thing, or with transcripts of the functional class or subset of said genes, or with the cDNA derived from the functional class or subset of said genes.

53. The method of claim 49, 50 or 51 wherein the living thing is a human.

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54. The method of claim 49, 50 or 51 wherein the living thing is a fungus.

55. The method of claim 49, 50 or 51 wherein the living thing is a eukaryote.

56. A method for producing an output signal data structure database recording the effect of subjecting a living thing to a plurality of stimuli comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the plurality of units confines a probe comprising a pre-determined sequence of nucleotides, and wherein each of said pre-determined sequences is hybridizable with a different identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

(b) transducing the physical signals into electrical output signals,

(c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

(d) repeating steps of detecting, transducing, and storing for a plurality of stimuli to form an output signal data structure database.

57. The method of claim 56 wherein the stimuli comprise basal conditions.

58. The method of claim 56 wherein the probes are 24-240 nucleotides in length.

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59. The method of claim 56 wherein the probes comprise nucleotide sequences selected so as to be hybridizable with a transcript of one or more of the identified genes, or with cDNA derived from one or more of the identified genes.

60. The method of claim 56 wherein the gene transcripts or cDNA derived from the living thing are labeled.

61. The method of claim 56 wherein the polynucleotide sequence of each probe is not hybridizable to more than one contiguous gene of the living thing.

62. The method of claim 56 wherein the ordered units in a probe matrix comprise an ordered array of units identified by X and Y coordinates, and wherein output signal data structures comprise matrices with elements identified by the X and Y coordinates.

63. The method of claim 56 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

64. The method of claim 63 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 5% of the genes of said living thing, or with transcripts of at least 5% of said genes, or with the cDNA derived from at least 5% of said genes.

65. The method of claim 64 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 50% of the genes of said living thing, or with transcripts of at least 50% of said genes, or with the cDNA derived from at least 50% of said genes.

66. The method of claim 63, 64 or 65 wherein the living thing is a human.

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67. The method of claim 63, 64 or 65 wherein the living thing is a fungus.

68. The method of claim 63, 64 or 65 wherein the living thing is a eukaryote.

69. A tangible computer memory storing:

(a) an output data structure database produced by the method of claim 56, said output data structure database comprising a plurality of stored digital signals, wherein each stored digital signal is associated with (i) a stimulus and (ii) with the identity of an identified gene and;

(b) one or more sequences of instructions, which, when executed by one or more processors, causes the processors to perform a comparison function for comparing output signal data from a probe matrix with the data stored in the output structure database of step (a).

70. A method for determining a response profile for a stimulus comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the plurality of units confines a probe comprising a pre-determined sequence of nucleotides, and wherein each of said pre-determined sequences is hybridizable with a different identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

(b) transducing the physical signals into electrical output signals,

(c) storing in digital form each electrical output signal in a stimulus response data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

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(d) determining a response profile for the stimulus by comparing the stimulus response data structure with a basal response data structure produced by carrying out the steps of detecting, transducing, and storing as above except that the probe matrix contacted with gene transcripts or cDNA derived from said living thing is subjected to basal conditions.

71. The method of claim 70 wherein the step of comparing comprises subtracting the elements of the stimulus response data structure and the basal response data structure.

72. The method of claim 70 wherein the step of comparing comprises dividing the elements of the stimulus response data structure and the basal response data structure.

73. The method of claim 70 wherein the probes are 24-240 nucleotides in length.

74. The method of claim 70 wherein the probes comprise lengths of nucleotide sequences selected so as to be hybridizable with a transcript or cDNA derived from a identified gene.

75. The method of claim 70 wherein the probes comprise polynucleotide sequences not hybridizable to more than one contiguous gene of the living thing.

76. The method of claim 70 wherein the gene transcripts or cDNA derived from the living thing are labeled.

77. The method of claim 70 wherein the ordered units in a probe matrix comprise an ordered array of units identified by X and Y coordinates, and wherein output signal data structures comprise matrices with elements identified by the X and Y coordinates.

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78. The method of claim 70 wherein the step of storing further comprises storing each digital signal in a computer readable memory

79. The method of claim 70 wherein the probe matrix comprises oligonucleotide probes that are arrayed on a substrate.

80. The method of claim 70 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

81. The method of claim 80 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 5% of the genes of said living thing, or with transcripts of at least 5% of said genes, or with the cDNA derived from at least 5% of said genes.

82. The method of claim 81 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 50% of the genes of said living thing, or with transcripts of at least 50% of said genes, or with the cDNA derived from at least 50% of said genes.

83. The method of claim 80, 81 or 82 wherein the living thing is a human.

84. The method of claim 80, 81 or 82 wherein the living thing is a fungus.

85. The method of claim 80, 81 or 82 wherein the living thing is a eukaryote.

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IX. EVIDENCE APPENDIX

None.

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X. RELATED PROCEEDINGS APPENDIX

None.

Respectfully submitted,

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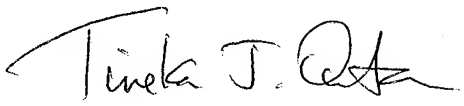

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